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Enantioselectively functionalised phenytoin derivatives by auxiliary-directed N to C aryl migration in lithiated α-amino nitriles

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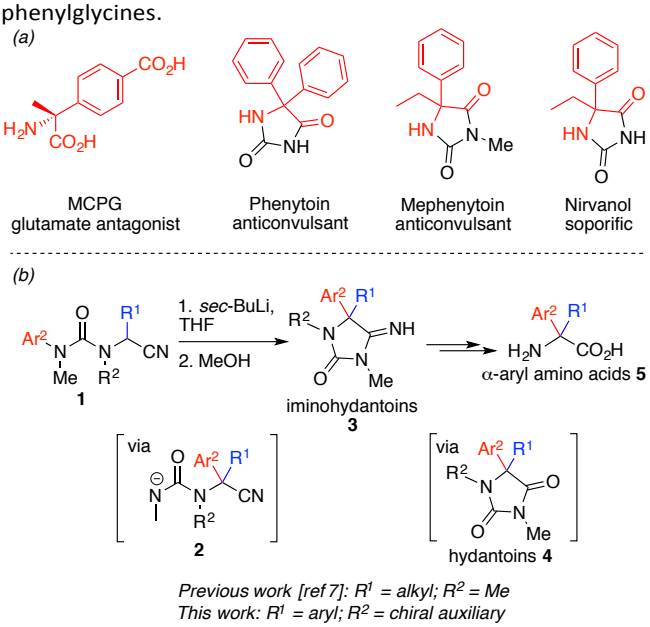
Lithiation of N'-arylureas derived from amino nitriles incorporating a *(1R, 2R)*-2-aminocyclohexanol chiral auxiliary leads to diastereoselective migration of the aryl ring to the position α to the nitrile. The resulting N'-lithiated ureas undergo spontaneous cyclisation to iminohydantoins, which may be hydrolysed to give chiral 5,5-diarylhydantoins related to phenytoin, in enantioenriched form.

α-Aryl quaternary amino acid motifs form components of several biologically active compounds, especially in the form of their 5,5-diaryl hydantoin derivatives (Scheme 1a).[1] In addition to this, the role of this motif in controlling the conformation of peptidomimetics[2] makes the stereoselective α-arylation of amino acids an important synthetic challenge. A number of approaches have been taken towards this aim, typically using S_NAr reactivity of highly electrophilic aryl rings or arynes towards nucleophilic enolate equivalents.[2b,3] Nonetheless, the stereoselective arylation of phenylglycine and other arylglycines[4] remains an unsolved problem, with the few reported routes to chiral α,α-diaryl glycines being characterized by diminished stereoselectivity or reactivity relative to their α-alkyl tertiary amino acid counterparts.[3-5]

One approach to the arylation of α-amino acids entails the use of an unusual electronically unactivated Smiles-like rearrangement that takes place within anionic or organometallic derivatives of *N'*-aryl ureas.[2b,3a,3b,6,7] We showed for example that the urea derivatives of amino nitriles **1**, when deprotonated, undergo racemic intramolecular *N'→C* aryl transfer to **2**, leading to arylated iminohydantoins **3** after spontaneous cyclisation.[7] Similar rearrangements of aminoamides and aminoesters have been rendered asymmetric by the use of chiral auxiliaries[2b,3a] or chiral memory,[3b] but these reactions failed to give products when highly hindered substrates such as phenylglycine were used as starting materials. We envisaged that the incorporation of a chiral auxiliary as R^2 in phenylglycine-derived amino nitriles **1** having an aromatic substituent R^1 might enable a diastereoselective arylation of ureas **1,** thereby giving access to enantiomerically enriched iminohydantoins **3** (Scheme 1b).[8] These are immediate precursors of both hydantoins **4** and amino acids **5**, which may be revealed by hydrolysis.[9] The method would furthermore be independent of the configuration of the amino acid moiety, making it particularly applicable to non-proteinogenic amino acids such as phenylglycines.



Scheme 1. (a) Bioactive α-aryl quaternary amino acids and hydantoin derivatives; (b) A published method for the synthesis of α-aryl quaternary amino acids and hydantoins by intramolecular arylation of aminonitrile ureas **1**.

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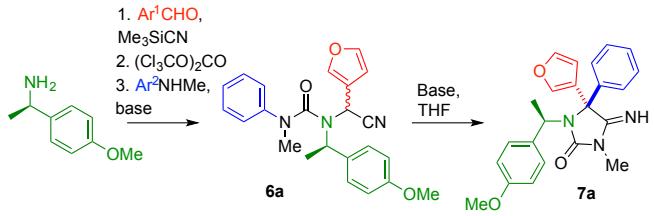
Electronic Supplementary Information (ESI) available: experimental details and characterisation and spectroscopic data for new compounds. See DOI: 10.1039/x0xx00000x

In order to explore this proposal with an amino-acid derivative bearing 'unnatural' substituents, a trial urea **6a** was made as a 1:1 mixture of diastereoisomers from optically pure (*R*)-1-(4-methoxyphenyl)ethylamine in a 3 step sequence involving a Strecker reaction,[10] *N*-phosgenation of the resulting aminonitrile, and urea coupling with *N*-methylaniline. The generality and simplicity of this Strecker approach to the starting materials illustrates a further advantage of using amino nitriles substituted at this position. Initial optimisation of the arylation reaction was carried out using this furan-substituted nitrile **6a** (Table 1). Several different bases deprotonated the starting material α to the nitrile function and promoted rearrangement and cyclisation to the α-arylated iminohydantoin product **7a**, generally in good yield. *sec*-BuLi gave poor selectivity (entries 1,2), and among the other bases LDA performed best, with optimal yield and selectivity being obtained in the absence of an additive: entry 7 shows a yield of 93% with 77:23 dr.

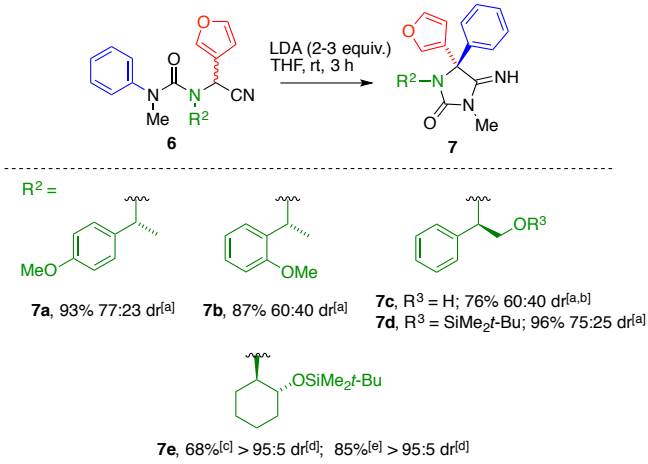
Table 1. Optimisation of reaction conditions using **6a**.



Entry	Base[a]	Additive	*t* /h, T / °C	**7a** yield /%[b] (dr)[b,c]
1	*sec*-BuLi	DMPU[d]	16, –50	88 (57:43)
2	LDA	DMPU[d]	6, 0	90 (67:33)
3	LDA	LiCl[e]	6, 0	83 (74:26)[f]
4	LDA	LiCl[e]	3, rt	91 (76:24)
5	LiTMP	LiCl[e]	3, rt	76 (75:25)
6	LiHMDS	LiCl[e]	16, rt	90 (74:26)
7	LDA	-	3, rt	93[g] (77:23)
8	KHMDS	-	12, rt	86 (67:33)

[a] Base (2.0 equiv. added to **6a** in THF). [b] Yield and dr determined by ^{1}H NMR of the crude reaction mixture using hexamethylbenzene as internal standard. [c] Absolute configuration of new stereogenic centre not determined. [d] DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 10% v/v. [e] 4 equiv. of dry LiCl added. [f] 7% **6a** recovered as a 50:50 mixture of diastereoisomers. [g] Isolated yield of a mixture of diastereoisomers in a 65:35 ratio.

The next challenge was to increase the diastereoselectivity of the reaction. A series of substrates **6b-6e** were made as diastereoisomeric mixtures from enantiopure primary amines (H_2N–R^2; highlighted in green) by the Strecker route used for **6a** (Scheme 2). Substrates **6b-c** containing chiral amines with additional metal-coordinating sites[11] were detrimental for both selectivity and yield. Protection of the free hydroxyl group of **6c** in the form of the *O*-*tert*-butyl(dimethyl)silyl derivative **6d** led to an increase in dr. Finally, the less flexible *trans*-2-aminocyclohexanol-derived substrate **6e** turned out to be the most selective by far, giving the iminohydantoin **7e** with a diastereoselectivity of >95:5. Repeating the reaction with both diastereosiomers individually gave the same selectivity. *Trans*-2-aminocyclohexanol has been used as a chiral auxiliary or chiral ligand in a number of other reactions,[12] and both enantiomers are commercially available and equally accessible on scale from amination of the corresponding meso epoxide.[12,13] The auxiliary may be easily removed under acidic conditions by dehydration – enamide hydrolysis.



Scheme 2. Screening chiral amines as auxiliaries. 2 equiv LDA used unless otherwise indicated. Diastereoisomeric ratios determined by ^{1}H NMR of crude reaction mixtures. [a] Absolute configuration of new stereogenic centre not determined. [b] 3 equiv LDA. [c] Yield from diastereoisomer 1. [d] Absolute configuration of **7e** (Ph ring migrates) assigned as shown by analogy to **9b** (see below). [e] Yield from diastereoisomer 2.

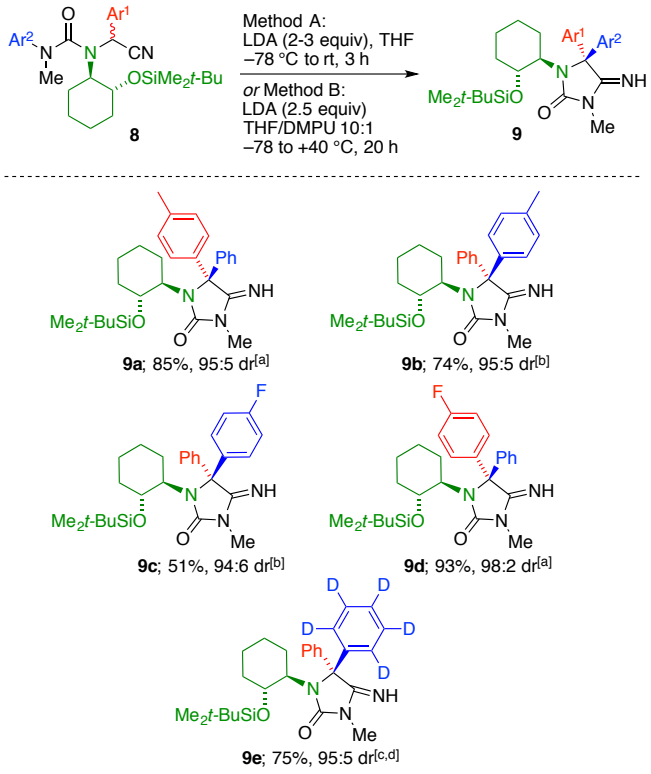
Extension of the highly diastereoselective rearrangement of **6e** to other substrates would constitute a method for the synthesis of enantiomerically enriched 5,5-diaryl hydantoins related to the anti-convulsant drug phenytoin, selectively functionalised on one of the two phenyl rings.[14] Such enantioselectively functionalised structures have found extensive in explorations of mechanisms of biological oxidation of this drug, but have been previously accessible in enantiopure form only by resolution.[15] To explore the application of the diastereoselective arylation to the asymmetric synthesis of phenytoin derivatives and other chiral 5,5-diarylhydantoins, we made a series of ureas **8a-e** bearing the optimal silylated (1*R*, 2*R*)-aminocyclohexanol auxiliary using the Strecker-type protocol employed for the synthesis of **6a-e** (see supporting information).

A pair of diastereoisomeric 4- and 4'-methylated phenytoin derivatives was made by migrating respectively a phenyl group to the α-position of the *p*-tolyl substituted urea **8a** and a *p*-tolyl group to the α-position of the phenyl substituted urea **8b**. Both reactions proceeded with excellent diastereoselectivity, and gave phenytoin derivatives **9a** and **9b** of opposite absolute configuration at the quaternary centre. On the basis that the new stereogenic centre of **9b** has *S* configuration (see below) we deduce that the (1*R*, 2*R*)-aminocyclohexanol induced migration to the *Si* face of the intermediate enolate. The phenyl group migrated in this intramolecular S_NAr reaction

somewhat more readily than the *p*-tolyl group, which required DMPU as co-solvent and heating to +40 °C to reach completion.

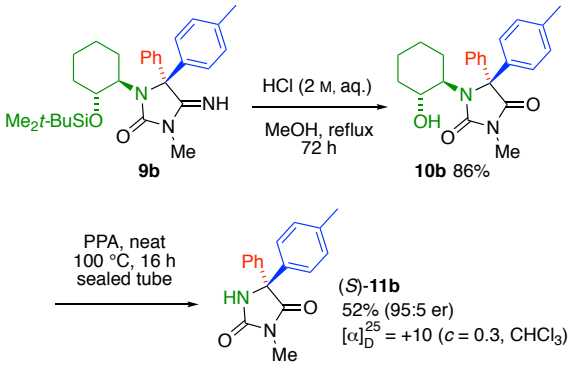
A second pair of diastereoisomeric fluorinated phenytoin derivatives was made by migrating either the 4-fluorophenyl group of **8c** or the phenyl group of **8d**, giving the enantioselectively fluorinated derivatives **9c** and **9d**. Again the substituted 4-fluorophenyl ring required more forcing conditions to migrate.

This diastereoselective arylation is of particular strategic value for the synthesis, in an enantioselective manner, of diaryl glycine derivatives in which the aryl rings are only minimally different, and would therefore be impossible to resolve using standard techniques. Illustrating this point, migration of the 2,3,4,5,6-pentadeuterophenyl ring to the phenyl-bearing nitrile substrate **8e** gave a product in which the phenytoin moiety is enantioselectively deuterated in only one of the two rings.[16]



Scheme 3. Asymmetric synthesis of phenytoin derivatives. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. [a] Method A; [b] Method B; [c] Diastereoisomeric ratio established by the relative integration of the two quaternary carbon signals showing HMBC correlations to a protonated (ie, non-deuterated) phenyl ring. [d] Using Method A but left to stir overnight.

Transformation of the diaryl iminohydantoins **9** into the valuable hydantoin products **10** was achieved by a two-step hydrolysis process in which the iminohydantoin was first desilylated and converted to a hydantoin and, and then in a second step the auxiliary removed. Scheme 4 shows this proves for the iminohydantoin **9b**. Acidic hydrolysis with 2M HCl in MeOH yielded *O*-desilylated hydantoin **10b** in high yield. Cleavage of the chiral auxiliary by heating in neat polyphosphoric acid afforded enantioenriched hydantoin **11b** in 52% yield with 95:5 *er*. The absolute configuration of (*S*)-**11b** was determined by comparison of its HPLC retention time on a chiral stationary phase with that of an authentic sample[17] (see SI for further details).



Scheme 4. Conversion of products into enantioenriched *C*-diaryl hydantoins.

The mechanism by which the intramolecular arylation takes place is an unactivated Smiles-like rearrangement[18] induced by the well-defined conformation[19] of the *N*-aryl urea.[20] This family of reactions do not require electron-withdrawing groups for success,[3a,3b,6a,6b,7,9] and appear to proceed by a single step pathway without a Meisenheimer intermediate.[20,21]

In summary, the diastereoselective intramolecular *C*-arylation of α-amino nitrile derivatives of phenylglycines gives, with high levels of stereoselectivity, α,α-diarylated hydantoin detivatives. The reaction was applied to the synthesis of fluorinated and deuterated derivatives of the drug phenytoin, of value in drug metabolism and pharmacokinetics studies, producing these derivatives with excellent yields and stereoselectivities.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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One sentence summary:

A 'non-classical' diastereoselective intramolecular SNAr reaction allows the construction of chiral diarylglycine derivatives in the form of hydantoins related to phenytoin

Graphical abstract: